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PALLENBERG, Alexander, J. [US/US]; 20024-330th
Avenue, N.E., Duvall, WA 98019 (US).

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(74) Agents: SEIDMAN, Stephanie, L. et al.; Heller Ehrman
White & McAuliffe LLP, 4350 La Jolla Village Drive, 7th
Floor, San Diego, CA 92122-1246 (US).

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(71) Applicants (*for all designated States except US*):
HEALTH RESEARCH, INC. [US/US]; Elm and Carlton
Streets, Buffalo, NY 14263 (US). LIGHT SCIENCES
CORPORATION [US/US]; 34931 SE Douglas Street,
Suite 200, Snoqualmie, WA 98065 (US).

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(72) Inventors; and

(75) Inventor/Applicants (*for US only*): PANDEY, Ravin-
dra, K. [US/US]; 75 Lemay Court, Williamsville, NY
14221 (US). DOUGHERTY, Thomas, J. [US/US]; 2306
West Oakfield Road, Grand Island, NY 14072 (US).

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(54) Title: EFFICIENT SYNTHESIS OF PYROPHEOPHORBIDE A AND ITS DERIVATIVES

(57) Abstract: A process for the preparation of pyropheophorbide a and its derivatives, including 3-devinyl-3-(1'-hexyloxy)ethyl--
pyropheophorbide-a, otherwise known as HPPH, is provided. The process involves treating chlorin *a*₈, in the form of its trimethyl
ester, with a base, followed by heating to give pyropheophorbide a, which is converted to HPPH by treatment with acid, followed by
hexyl alcohol under basic conditions.

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EFFICIENT SYNTHESIS OF PYROPHEOPHORBIDE A AND ITS DERIVATIVES

RELATED APPLICATIONS

Priority is claimed herein to U.S. provisional patent application No.
5 60/393,617, filed July 2, 2002, to Pandey *et al.*, entitled "EFFICIENT
SYNTHESIS OF PYROPHEOPHORBIDE A AND ITS DERIVATIVES." For
U.S. national stage purposes and where appropriate, the above-referenced
application is incorporated herein by reference in its entirety.

FIELD

10 Provided herein is a process for the preparation of pyropheophorbide a
and its derivatives, including hexyloxy pyropheophorbide a, otherwise known
as HPPH. The process involves treating chlorin *e*₆, in the form of its trimethyl
ester, with a base, followed by heating to give pyropheophorbide a, which is
converted to HPPH by treatment with hexyl alcohol under acidic conditions.

15 BACKGROUND

Photodynamic therapy (PDT) is relatively a new treatment method for
the destruction of tumors. PDT is based on the accumulation in malignant
tissue of a photosensitizer after its administration. Subsequent illumination
with light of an appropriate wavelength creates a photochemical reaction, a
20 so-called photodynamic effect (photochemical reaction producing singlet
oxygen) that results in tumor destruction.

It is well established that both absorption and scattering of light by
tissue increases as the wavelength decreases, and that the most effective
sensitizers are those that have strong absorption bands between 660-800 nm.
25 In recent years, a series of photosensitizers have been developed related to
pyropheophorbide-a and purpurinimides (obtained from purpurin-18) with a
variable lipophilicity exhibiting the longer wavelength absorption at 665 and
705 nm (*in vivo* absorption) respectively.

Historically, preparation of HPPH has required the isolation of methyl
30 pheophorbide a from *Spirulina Algae* by cryogenic fracturing of the cells
followed by extraction, chromatographic purification, and recrystallization.

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See, e.g., U.S. Patent No. 5,198,460 and references cited therein. The methyl pheophorbide a obtained in this way was then separately subjected to thermal decarboxylation in collidine at reflux temperature. Following this treatment, the resulting methyl pyropheophorbide a was treated with hexyl alcohol and acid
5 to form the hexyl ether moiety. Finally, the methyl ester was removed by saponification to give HPPH. Thus, four rather laborious steps were required in order to obtain HPPH. This procedure works well in the laboratory scale preparation where the final product is required in small amounts. However, the purification of the intermediates at several stages of the synthesis requires
10 column chromatography. Therefore, there is a need for an alternate synthesis of HPPH suitable for large-scale synthesis.

SUMMARY

Provided herein is a synthetic process for the preparation of hexyloxy pyropheophorbide a and related compounds. The process is suitable for
15 large scale (i.e., multigram to multi-kilogram or more) production of such compounds.

The process provided herein affords the desired product in higher yield and/or purity than known processes. Also, the process provided herein avoids the use of chromatographic purification of intermediates and/or desired
20 product.

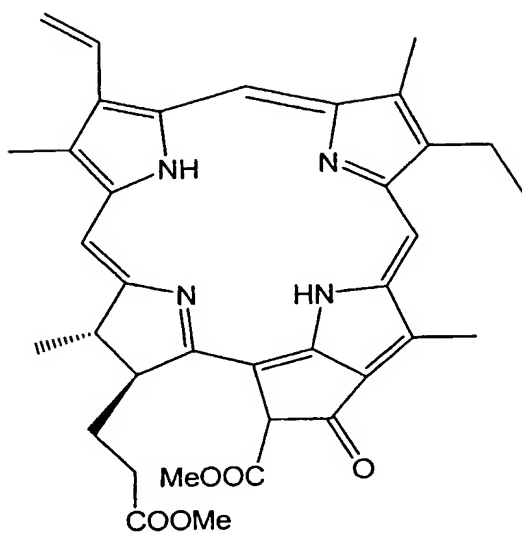
DETAILED DESCRIPTION

A. Definitions

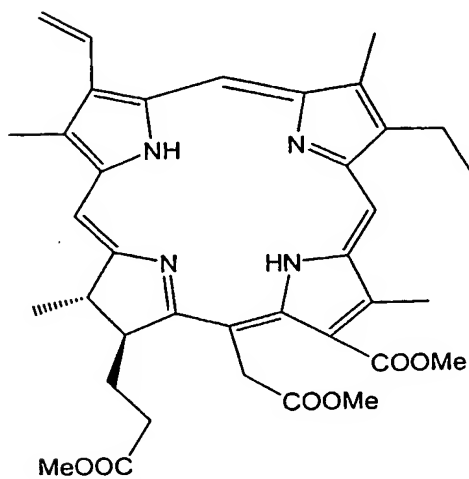
Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in
25 the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, "methyl pheophorbide a" refers to:

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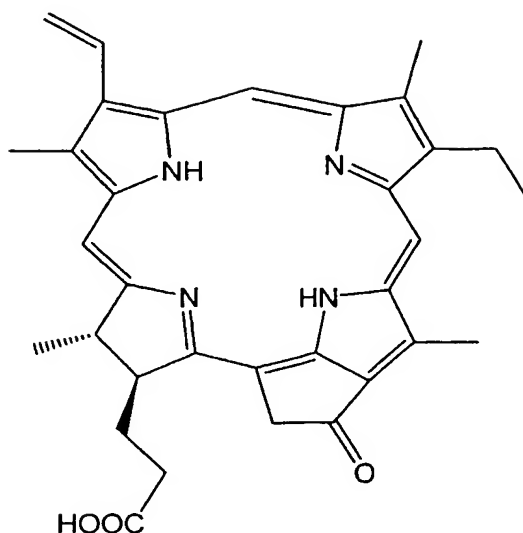
As used herein, "chlorin e6 trimethyl ester" refers to:



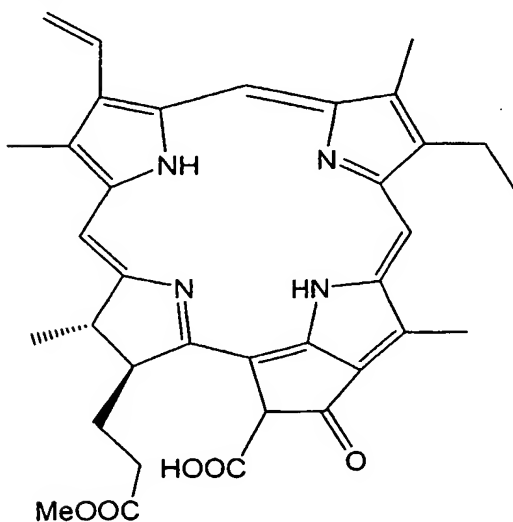
As used herein, an "aromatic solvent" is an organic compound having
5 an aromatic nucleus.

As used herein, "pyropheophorbide a" refers to:

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As used herein, a "high boiling aromatic solvent" refers to an aromatic solvent, as defined herein, that has a boiling point high enough to effect decarboxylation of the following compound at reflux:

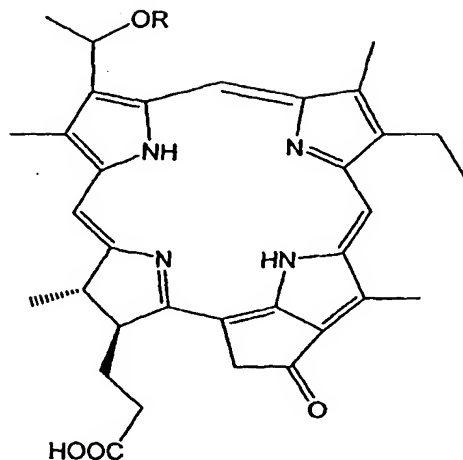


5 MeOOC

In certain embodiments herein, the boiling point of a high boiling aromatic solvent is greater than 115 °C, 120 °C, 125 °C, 130 °C, 135 °C, 140 °C, 145 °C, 150 °C, 155 °C, 160 °C, 165 °C or 170 °C.

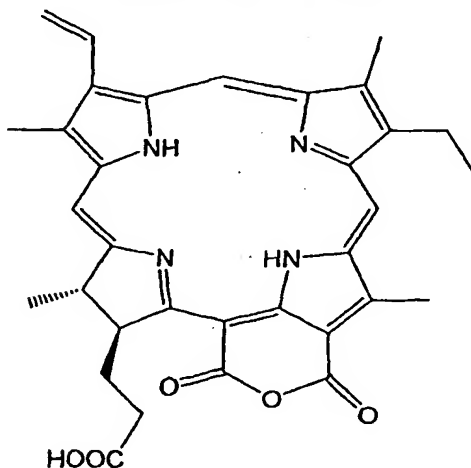
As used herein, "ether analogs of pyropheophorbide a" refers to
10 compounds of the general formula:

-5-



where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

As used herein, "purpurin-18" is:

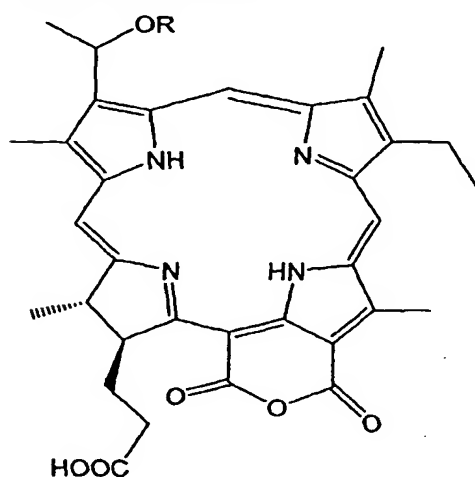


As used herein, a "base" is an inorganic or organic compound sufficiently basic to effect a Dieckmann condensation. In certain

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embodiments, the base is an organic compound. In other embodiments, the base has a pKa of the corresponding protonated form of less than about 15, 10, 8 or 5, relative to water.

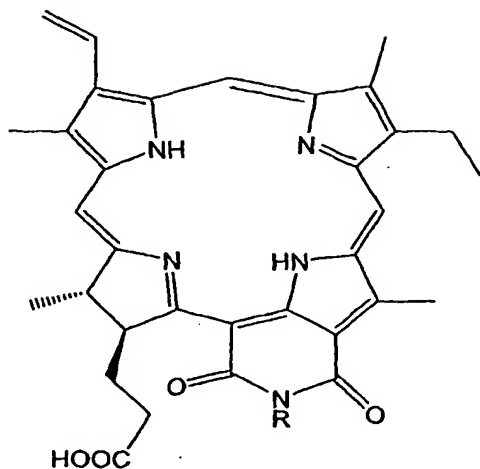
As used herein, "ether analogs of purpurin-18" refers to compounds of
5 the general formula:



where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl,
and is unsubstituted or substituted with one or more substituents, in one
embodiment one to five substituents, in another embodiment one, two or three
10 substituents, each independently selected from halo, pseudohalo, alkyl,
alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy,
aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

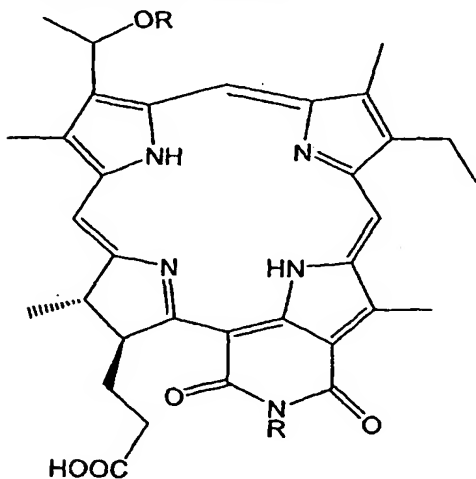
As used herein, a "purpurinimide" is a compound of the general
formula:

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where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

As used herein, "ether analogs of purpurinimides" refers to compounds of the general formula:



10

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where each R is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from

- 5 halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

As used herein, an "acid" is an inorganic or organic compound of sufficient acidity to effect addition of an alcohol to a vinyl group. In one
10 embodiment, an acid is an inorganic compound. In another embodiment, an acid has sufficient acidity to effect addition of an alcohol to a vinyl group directly attached to an aromatic porphyrin nucleus.

As used herein, the term "porphyrin" refers to a cyclic structure typically composed of four pyrrole rings, and refers to a porphyrin or porphyrin
15 derivative. Such derivatives include porphyrins with extra rings ortho-fused, or ortho-perifused, to the porphyrin nucleus, porphyrins having a replacement of one or more carbon atoms of the porphyrin ring by an atom of another element (skeletal replacement), derivatives having a replacement of a nitrogen atom of the porphyrin ring by an atom of another element (skeletal
20 replacement of nitrogen), derivatives having substituents other than hydrogen located at the peripheral (meso-, β -) or core atoms of the porphyrin, derivatives with saturation of one or more bonds of the porphyrin (hydroporphyrins, e.g., chlorins, bacteriochlorins, isobacteriochlorins, decahydroporphyrins, corphins, pyrrocorphins, etc.), derivatives obtained by
25 coordination of one or more metals to one or more porphyrin atoms (metalloporphyrins), derivatives having one or more atoms, including pyrrolic and pyrromethenyl units, inserted in the porphyrin ring (expanded porphyrins), derivatives having one or more groups removed from the porphyrin ring (contracted porphyrins, e.g., corrin, corrole) and combinations of the foregoing

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derivatives (e.g phthalocyanines, porphyrazines, naphthalocyanines, subphthalocyanines, and porphyrin isomers).

As used herein, "chlorin" refers to a class of porphyrin derivatives having a cyclic structure typically composed of four pyrrole rings having one
5 partially saturated pyrrole ring, such as the basic chromophore of chlorophyll.

As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 or 2 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds and alkenyl carbon chains
10 of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl,
15 isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl, allyl (propenyl) and propargyl (propynyl). As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 8 carbons.

As used herein, halogen refers to one of the electronegative elements
20 of group VIIA of the periodic table (fluorine, chlorine, bromine, iodine, astatine).

As used herein, "hydroxy group" generally refers to a hydroxyl group having the formula -OH.

As used herein, "carboxy" generally refers to the radical -C(O)OH.

25 As used herein, "ester group" generally refers to a substituent of the general formula -C-O-O-R¹ where R¹ may be either aliphatic or aromatic.

As used herein, "aromatic group" generally refers to a ring structure having cyclic clouds of delocalized π electrons above and below the plane of the molecule, where the π clouds contain $(4n+2)$ π electrons. A further
30 discussion of aromaticity is found in Morrison and Boyd, *Organic Chemistry*,

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(5th Ed., 1987), Chapter 13, entitled "Aromaticity," pages 477-497, incorporated herein by reference.

As used herein, "amide group" generally refers to the group - C(O)NRR where each R is independently aliphatic or aromatic.

5 As used herein, "amine group" has the general formula -NRR, where each R is independently any alkyl or aryl group.

As used herein, "cycloalkyl" refers to a saturated mono- or multi- cyclic ring system, in certain embodiments of 3 to 20 carbon atoms, in other embodiments of 3 to 10 carbon atoms. The ring systems of the cycloalkyl
10 groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion.

As used herein, "aryl" refers to aromatic monocyclic or polycyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as unsubstituted or substituted fluorenyl, unsubstituted
15 or substituted phenyl, and unsubstituted or substituted naphthyl.

As used herein, "heteroaryl" and "heteroaromatic group" refers to a monocyclic or polycyclic aromatic ring system, in certain embodiments, of about 5 to about 20 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than
20 carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, quinolinyl and isoquinolinyl.

25 As used herein, "heterocyclyl" refers to a monocyclic or polycyclic non-aromatic ring system, in one embodiment of 3 to 20 members, in another embodiment of 4 to 10 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but
30 not limited to, nitrogen, oxygen or sulfur. In embodiments where the

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heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, acyl, guanidino, or the nitrogen may be quaternized to form an ammonium group where the substituents are selected

5 as above.

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

10 As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, 15 trifluoromethoxy, and azide.

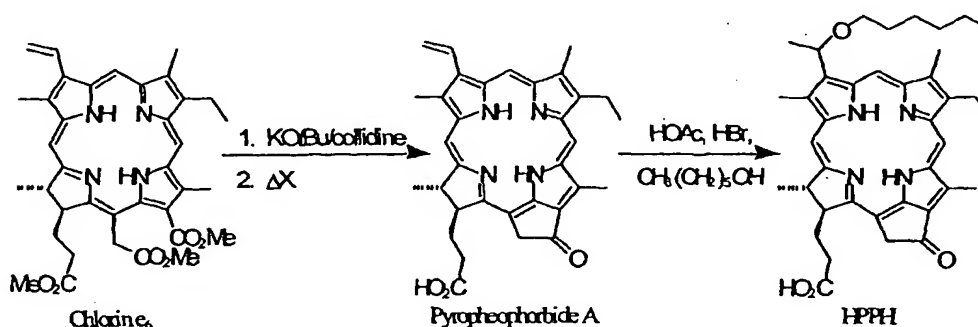
All chemical compounds include both the (+) and (-) stereoisomers, as well as either the (+) or (-) stereoisomer, and also all diastereomers, rotamers and geometric isomers.

B. Process for Preparing Pyropheophorbide a and its derivatives

20 The process provided herein, depicted below, avoids a number of shortcomings of the prior art by resorting to another source as the raw material. Chlorin *e*₆ trimethyl ester undergoes a Dieckmann Condensation to form the additional exocyclic ring, sometimes called an "E-ring", which is present in the pheophorbides, and chlorophyll itself for that matter. See, *e.g.*,
25 Schaefer, J.P.; Bloomfield, J.J. *Org. React.* **1967**, *15*, 1-203; and Davis, B.R.; Garrett, P.J. *Comp. Org. Syn.* **1991**, *2*, 806-829. This reaction has traditionally been performed in aromatic solvents, originally benzene, but later toluene and others for safety reasons. In the case of chlorin *e*₆ and compounds like it, pyridine has been used for this purpose. See, *e.g.*, Smith,
30 K.M.; Bisset, G.M.F.; Bushell, M.J. *J. Org. Chem.* **1980**, *45*, 2218-2224. These

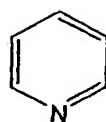
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workers did not use chlorin e_6 itself, but a similar compound in which a methyl group substituent was present at position 5, the δ "meso" position.

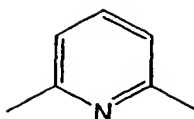


- In order to improve the performance of this reaction, the pyridine was
- 5 replaced with a more substituted analog in order to raise the boiling point of the reaction mixture. Thus, collidine, also called *sym*-collidine (for symmetrical, see below) or 2,4,6-trimethylpyridine, was used. Other basic aromatic solvents, including but not limited to 2,6-lutidine, could also be used. In this way the temperature of reflux of the reaction mixture is altered - the
- 10 boiling point of pyridine is 115 °C, while that of collidine is 172 °C. By raising the temperature of the reaction mixture after completion of the Dieckmann Condensation, it is possible to bring about the subsequent thermal decarboxylation without any intervening purification or unnecessary manipulation of the reaction mixture. As a further benefit, it was found that,
- 15 under the strongly basic conditions employed to carry out the Dieckmann Condensation, the methyl ester of the pheophorbide system also undergoes cleavage, thus accomplishing three chemical transformations in a single treatment.

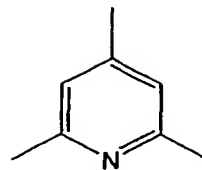
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Pyridine
Bp 115 °C
 $pK_a = 5.17$



2,6-Lutidine
Bp 144 °C
 $pK_a = 6.71$



sym-Collidine
Bp 172 °C
 $pK_a = 7.43$

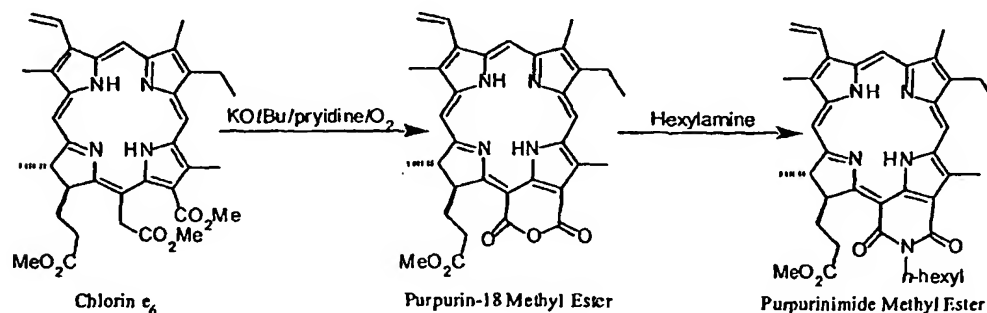
Basic aromatic solvents

The pheophorbide a obtained in this way need only be converted to its hexyl ether in order to produce HPPH. This can be done in much the same way as it was done in the older synthesis, giving an overall two-pot

5 preparation of this product.

Since many other compounds can also be obtained from pyropheophorbide a (see below), this new process affords greatly simplified access to all such compounds. These compounds include purpurin-18 and its derivatives, especially the ethers made from the vinyl group in an analogous manner to the hexyl ether in HPPH, and the purpurinimide series. In these

10 examples, one would omit the high temperature treatment and thermal decarboxylation in order to retain the carboxyl group for the construction of the expanded E-ring used in these systems.



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EXAMPLE 1**Preparation of pyropheophorbide-a**

Chlorin e_6 trimethyl ester (350 mg) was dissolved in dry 2,4,6-collidine (30 mL) and then carefully degassed with nitrogen at 50°C under vacuum.

- 5 Potassium *tert*-butoxide (Aldrich, 5.0 mL, 1 M) was added. The initial bright green color immediately turned orange and the reaction mixture was left stirring at room temperature for 20 min. It was then quenched with degassed glacial acetic acid (10 mL). The flask was then connected to a small distillation assembly (condenser, receiving head and a flask), the acetic acid along with a
- 10 small amount of collidine (5 mL) were removed under high vacuum. The distillation assembly was dismantled and fresh collidine (15 mL) was added. The reaction flask was then connected to a condenser, and the reaction mixture was heated at reflux under nitrogen for 2 hours. The solvent was removed under high vacuum. The residue so obtained was re-dissolved in
- 15 dichloromethane (100 mL), washed with water (2 × 100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent gave pyropheophorbide-a (as carboxylic acid) in 85% yield after crystallization. ^1H NMR (CDCl_3 , δ ppm): 9.35 and 9.15 and 8.50 (each s, 1H, meso H); 7.80 (m, 1H, $\text{CH}=\text{CH}_2$); 6.25, 6.10 (each d, 1H, $\text{CH}-\text{CH}_2$); 5.22 (dd, 2H, $-\text{CH}_2$, exocyclic
- 20 ring); 4.41 (q, 1H, 18H); 4.28 (d, 1H, 17-H); 3.75 (q, 2H, CH_2CH_3 merged with one of the ring CH_3); 3.62, 3.35 and 3.10 (each s, 3H, ring CH_3); 2.80-2.10 (several m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$); 1.80 (d, 3H, 18- CH_3); 1.60 (t, 3H, CH_2CH_3); -1.78 (each s, 1H, NH).

EXAMPLE 2**25 3-Devinyl-3-(1'-hexyloxy)ethyl-pyropheophorbide-a (HPPH)**

- Pyropheophorbide-a (100 mg) was taken in a 50 mL round bottom flask and 30% HBr/HOAc (Aldrich, 2.0 mL) was added. The reaction mixture was stirred at room temperature for 2 hour and the solvent was removed under high vacuum (bath temperature was maintained at 30-40°C). It was re-
- 30 dissolved in dry dichloromethane (10 mL). Hexanol (2.00 mL), potassium

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carbonate (200 mg) were added, and the reaction mixture was stirred at room temperature for 45 min under nitrogen atmosphere. It was poured in water (100 mL), extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent
5 gave a residue that was crystallized from dichloromethane/ hexane in 71% yield; ¹H NMR (CDCl₃, δ ppm): 9.77 and 9.52 8.50 (s, 1H, *meso*-H); 5.90 [q, 1H, CH(*o*-hexyl)-CH₃]; 5.22 (dd, 2H, 2H, exocyclic ring); 4.41 (q, 1H, 18H); 4.28 (d, 1H, 17-H); 3.75 (q, 2H, CH₂CH₃); 3.62, 3.25 and 3.20 (each s, 3H, ring CH₃); 2.10 (3H, CHCH₃); 1.80 (d, 3H, 18-CH₃); 1.75 (t, 3H, CH₂CH₃);
10 2.75-2.12 (several m, CH₂CH₂CO₂H); 0.76-1.30 [several m, 10H, (CH₂)₅] 0.43 and -1.78 (each s, 1H, NH). Mass calculated for: C₃₉H₄₈N₄O₄: 636. Found: 637 (M + 1).

EXAMPLE 3

Preparation of Purpurin-18 methyl ester

15 Chlorin e₆ trimethyl ester (175 mg) was dissolved in pyridine (15 mL) and the reaction temperature was maintained at 50°C. A slow stream of air was passed through the solution and potassium *tert*-butoxide (Aldrich, 2.5 mL, 1.0 M) was added. The reaction mixture was stirred at room temperature for 20 min. It was quenched with glacial acetic acid (5 mL), poured in water,
20 extracted with dichloromethane (2 × 100 mL). The dichloromethane layer was washed with 2 M HCl (50 mL), then washed with water again. The organic layer was separated and dried over anhydrous sodium sulfate. The residue obtained after evaporating the solvent was re-dissolved in dichloromethane, treated with diazomethane, purified by silica column chromatography, eluting
25 with 2% acetone in dichloromethane and crystallized from dichloromethane/hexane. Yield 80%; ¹H NMR (CDCl₃, δ ppm): 9.60, 9.35 and 8.60 (each s, 1H, *meso*-H); 7.90 (m, 1H, CH=CH₂); 6.30 and 6.20 (each d, 1H, CH=CH₂); 5.12 (d, 1H, 17-H); 4.40 (q, 1H, 18-H); 3.75 (s, 3H, CO₂CH₃); 3.65 (q, 2H, -CH₂CH₃); 3.60, 3.30 and 3.15 (each s, 3H, ring CH₃); 2.80-1.90

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(several m, $-CH_2CH_2CO_2CH_3$); 1.75 (d, 3h, 18- CH_3); 1.60 (t, 3H, $-CH_2CH_3$); 0.20 and -0.90 (each br s, 1H, NH).

Since modifications will be apparent to those of skill in this art, it is
5 intended that this invention be limited only by the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A process for the preparation of methyl pheophorbide a, comprising treating chlorin e₆ trimethyl ester with a base in an aromatic solvent.
- 5 2. A process for the preparation of pyropheophorbide a, comprising:
 - (a) treating chlorin e₆ trimethyl ester with a base in a high-boiling aromatic solvent to give methyl pheophorbide a; and
 - (b) heating the methyl pheophorbide a to effect decarboxylation and
- 10 saponification.
3. A process for the preparation of ether analogs of pyropheophorbide a, comprising:
 - (a) treating chlorin e₆ trimethyl ester with a base in a high-boiling aromatic solvent to give methyl pheophorbide a;
- 15
 - (b) heating of the methyl pheophorbide a to effect decarboxylation and saponification to give pyropheophorbide a; and
 - (c) treating the pyropheophorbide with an acid, followed by an alcohol under basic conditions to effect addition of the alcohol across a vinyl group.
- 20 4. The process of claim 3, wherein the alcohol is 1-hexanol (n-hexyl alcohol).
5. A process for the preparation of purpurin-18, comprising:
 - (a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18; and
- 25
 - (b) re-esterifying the resulting purpurin-18.
6. A process for the preparation of ether analogs of purpurin-18, comprising:
 - (a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18;
- 30
 - (b) re-esterifying the purpurin-18; and

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- (c) treating the re-esterified purpurin- 18 with an acid, followed by treating with an alcohol under basic conditions.
- 7. A process for the preparation of purpurinimides, comprising:
 - (a) treating chlorin e₆ trimethyl ester with a base in an aromatic
 - 5 solvent in the presence of air to give purpurin-18;
 - (b) re-esterifying the purpurin-18; and
 - (c) treating the re-esterified purpurin-18 with a primary amine.
- 8. A process for the preparation of ether analogs of purpurinimides, comprising:
 - 10 (a) treating chlorin e₆ trimethyl ester with a base in an aromatic solvent in the presence of air to give purpurin-18;
 - (b) re-esterifying the purpurin-18;
 - (c) treating the re-esterified purpurin-18 with a primary amine to give a purpurinimide; and
 - 15 (d) treating the resulting purpurinimide with an acid, followed by an alcohol under basic conditions.